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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

BENNEKER et al.

Appl. No.: CPA of 09/200,743

Filed: November 27, 2000

For: CRYSTALLINE PAROXETINE METHANE SULFONATE (as amended)

Art Unit: 1625

Examiner: Chang, C.

DECLARATION OF DR. MICHAEL T. CRIMMINS

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Michael T. Crimmins, Ph.D., hereby declare as follows:

1. In 1980, I received a Ph.D. in Organic Chemistry from Duke University, Durham, North Carolina. My thesis was entitled Synthetic Applications of Photoannelations. I. Valerolactones. II. The Alleged Genipic Acid. III. Sarracenin. From 1980 to 1981, I was a postdoctoral student at the California Institute of Technology. During that period, I carried out research in organic synthesis focused on the synthesis of naturally occurring ionophore antibiotics.

2. Since 1981, I have been employed by the University of North Carolina, Chapel Hill, North Carolina. I am presently a Professor of Chemistry, in which capacity I teach, conduct research and assist in administration of University programs. Over the course of my tenure at the University of North Carolina, I have taught undergraduate and graduate level courses and seminars in organic chemistry and advanced organic chemistry. I have also trained and supervised graduate and postdoctoral students, many of whom have gone on to careers as chemists and research scientists at major pharmaceutical and chemical companies.

3. Since 1976, I have been engaged in synthetic organic chemistry. A significant part of my research has dealt with the total synthesis and structural characterization of natural products of biological interest, including crystalline materials. I am familiar with and have regularly used a variety of qualitative and quantitative methods for ascertaining and/or comparing the identity and structure of organic materials. These methods include, for example, x-ray diffraction ("XRD"), solution and solid state proton and carbon-13 nuclear magnetic resonance ("NMR"), infrared spectrophotometry ("IR"), mass spectrometry ("MS"), high performance liquid chromatography ("HPLC") and optical rotation ("(α)").

4. I have authored or coauthored approximately eighty papers and thirty-five abstracts which describe my research in the area of synthetic organic chemistry. These papers have been published in numerous chemical journals, including Journal of the American Chemical Society, Journal of Organic Chemistry, Organic Letters, Tetrahedron Letters, Tetrahedron, Chemical Reviews, Syn Lett, Organic Reactions and Synthesis.

5. I have received research grants from nonprofit foundations and federal institutions, such as the National Institutes of Health and the National Science Foundation, as well as from major pharmaceutical and chemical companies. I have also received many academic and research awards and honors. These include an NIH-NCI Postdoctoral Fellowship, an Alfred P. Sloan Fellowship, an American Cyanamid Faculty Fellowship and an Arthur C. Cope Scholar Award.

6. Since 1981, I have served as a reviewer for a number of peer review publications. Presently, I am a manuscript referee for the following journals: Journal of the American Chemical Society, Journal of Organic Chemistry, Tetrahedron: Asymmetry, Organometallics, Canadian Journal of Chemistry, Synthetic Communications, Journal of Natural Products, Biorganic and Medicinal Chemistry, Biorganic and Medicinal Chemistry Letters, Journal of the Chemistry Society, Journal of the Chemical Society: Chemical Communications, Journal of Carbohydrate Chemistry,

Organic Letters, Tetrahedron Letters, Tetrahedron, Chemical Reviews, Syn Lett, Organic Reactions, Synthesis and Journal of Chemical Research.

7. A copy of my CV and list of publications is attached hereto as Tab A.

8. Attached hereto as Tab B is a copy of U.S. Patent 5,874,447 ("the '447 patent"). Column 7 of the '447 patent illustrates two syntheses of crystalline paroxetine methane sulfonate. The "Experimental" section, column 7, lines 17-40, refers to the preparation of a "seeding crystal" of paroxetine methane sulfonate. "Example 1," column 7, lines 44-60, refers to a larger scale preparation of paroxetine methane sulfonate, using the seed crystal.

9. Following the '447 patent, except as to minor adjustments, I have prepared two separate quantities of crystalline paroxetine methane sulfonate, the first based on the Experimental section and the second based on the Example 1 section. To confirm the identity and structure of these materials, I characterized each by infrared spectroscopy and x-ray powder diffraction.

10. Attached hereto as Tab C are copies of the pages from my notebook relating to my preparation of the "seeding crystal" of paroxetine methane sulfonate. As shown on the notebook pages, this first experiment was performed on essentially the same scale as in the Experimental section of the '447 patent. Attached hereto as Tab D is a copy of the page from my notebook relating to my preparation of a slightly larger scale quantity of crystalline paroxetine methane sulfonate. As shown on the notebook page, this second experiment was performed on a roughly one tenth scale of the scale in Example 1. The syntheses recorded in Tabs C and D reflect the first and only time I have prepared crystalline paroxetine methane sulfonate.

11. Attached hereto as Tabs E, F and G are IR spectrographs of the crystalline paroxetine methane sulfonate prepared as shown in Tab C. Attached hereto as Tabs H, I and J are IR spectrographs of the crystalline paroxetine methane sulfonate prepared as shown in Tab D. Included with each of Tabs E through J are four different

sheets. The first sheet is a complete spectrograph, spanning from 4000 to 500 cm^{-1}. The additional three sheets represent "expansions" of discrete portions of the complete spectrograph, namely, from 4000 to 1650 cm^{-1}; from 1650 to 1000 cm^{-1}; and from 1000 to 500 cm^{-1}. All of the IR spectrographs were generated on the same spectrometer, a Bomem, Michelson 120 Series FTIR Spectrometer, and all crystalline samples were prepared as potassium bromide disks. The IR spectrographs differ in their resolution and transmittance tolerance, which are instrumental variables which may be selected or adjusted to increase the definition of discrete peaks and the number of peaks selected to be printed as numerical values. The particular resolutions used were 8 cm^{-1} [Tabs E and H], 4 cm^{-1} [Tabs F and I] and 2 cm^{-1} [Tabs G and J]. The transmittance tolerance was 5 percent.

12. Attached hereto as Tab K is a copy of U.S. Patent 6,063,927 ("the '927 patent"). Claim 1 of the '927 patent reads "Paroxetine methanesulfonate in crystalline form having the following characteristic IR peaks: 1603, 1194, 1045, 946, 830, 601, 554, and 539 ±4 cm^{-1}."

13. Each of the crystalline paroxetine methane sulfonates I prepared has the eight IR peaks listed in claim 1 of the '927 patent, as shown by the following summary table.

'927 PATENT	TABS C, G (SEED)	TABS D, J (EXAMPLE 1)
1603 ±4 cm^{-1}	1604.80	1605.60
1194 ±4 cm^{-1}	1195.61	1193.01
1045 ±4 cm^{-1}	1045.44	1045.40
946 ±4 cm^{-1}	945.74	946.24
830 ±4 cm^{-1}	828.52	830.31
601 ±4 cm^{-1}	601.02	601.14
554 ±4 cm^{-1}	554.24	553.95
539 ±4 cm^{-1}	539.79	539.37

14. The '927 patent includes several examples which illustrate the synthesis of crystalline paroxetine methane sulfonate. Many of the examples include a list of IR peaks and x-ray powder diffraction peaks for the referenced crystalline materials. The crystalline paroxetine methane sulfonate of Example 4, prepared as a

potassium bromide disk, produced an IR spectrum having thirty five peaks. The complete IR of each of the crystalline paroxetine methane sulfonates I prepared is essentially identical to the complete IR of Example 4 of the '927 patent, as shown by the following summary table.

EXAMPLE 4	TABS C, G (SEED)	TABS D, J (EXAMPLE 1)
3006		
1638	1636.67	1637.77
1614	1616.80	1617.53
1604	1604.80	1605.60
1513	1512.02	1512.72
1499	1500.70	1499.90
1469	1470.13	1469.60
1422	1421.89	1421.61
1399	1399.01	1399.62
1358	1356.84	
1336	1337.47	1336.14
1278	1277.75	1278.20
1194	1195.61	1193.01
1163		
1144	1144.55	1144.94
1132	1133.00	1132.09
1095	1093.97	1093.59
1091		
1045	1045.44	1045.40
1034	1035.24	1033.92
946	945.74	946.24
927	927.58	927.21
916	916.12	916.24
870	869.86	870.39
830	828.52	830.31
822		822.57
787	786.52	786.85
776	776.23	775.53
766	765.92	
601	601.02	601.14
572	571.80	572.02
554	554.24	553.95
539	539.79	539.37
529	527.90	529.14
514	514.49	514.59

15. The few empty spaces in the Table above are not indicative of the absence of a peak in the relevant spectrum at the specified wavenumber. The spectrographs, particularly the relevant "expansion" sheets, show that peaks do indeed appear, they were just not printed out by the computer. The reason for this was that the spectrometer was set at a transmittance tolerance which simply did not generate a printed wave number.

16. Attached hereto as Tab L and Tab M, respectively, is an x-ray powder diffraction pattern and a related table listing peak diffraction angles and relative intensities of the crystalline paroxetine methane sulfonate prepared as shown in Tab C. Attached hereto as Tab N and Tab O, respectively, is an x-ray powder diffraction pattern and a related table listing peak diffraction angles and relative intensities of the crystalline paroxetine methane sulfonate prepared as shown in Tab D. The diffraction patterns were all generated on the same x-ray diffractometer, an instrument with a 1.5 KW x-ray tube with Cu-K α-radiation, a graphite monochrometer and a 2-D imaging plate detector.

17. Example 3 of the '927 patent [Tab K, column 11] lists thirty-five peaks appearing in an x-ray powder diffraction pattern of crystalline paroxetine methane sulfonate. Examples 4, 12, 14, 15, 16, 18, 19 and 20 state that the crystalline paroxetine methane sulfonate produced by the variously described procedures had the "same" x-ray powder diffraction pattern as in Example 3. The x-ray powder diffraction pattern of each of the crystalline paroxetine methane sulfonates I prepared is essentially identical to the x-ray powder diffraction pattern of Examples 3, 4, 12, 14, 15, 16, 18, 19 and 20 of the '927 patent, as shown by the following summary table.

'927 PATENT EXAMPLE 3		TABS C, L/M (SEED)		TABS D, N/O (EXAMPLE 1)	
Angle (2Θ)	Rel. Int. (%)	Angle (2Θ)	Rel. Int. (%)	Angle (2Θ)	Rel. Int. (%)
6.7	8.5	6.7	22.6	6.7	21.3
8.2	**46.5**	8.2	**73.4**	8.2	**76.3**
10.4	9.9	10.4	14.6	10.4	13.7
10.9	5.5	10.9	6.0	10.9	7.1
13.9	8.6	13.8	12.1	13.8	13.1

'927 PATENT EXAMPLE 3		TABS C, L/M (SEED)		TABS D, N/O (EXAMPLE 1)	
Angle (2Θ)	Rel. Int. (%)	Angle (2Θ)	Rel. Int. (%)	Angle (2Θ)	Rel. Int. (%)
14.7	7.1	14.6	7.4	14.6	8.8
15.6	8.2	15.5	7.4	15.6	8.8
16.3	15.8	16.2	20.3	16.2	21.5
17.7	**39.6**	17.6	**34.6**	17.6	**35.1**
18.2	**93.9**	18.2	**98.2**	18.2	**100.0**
19.8	9.0	19.8	10.7	19.8	12.1
20.5	**23.0**	20.4	**25.6**	20.4	**28.5**
21.5	**50.2**	21.5	**47.2**	21.4	**48.9**
21.9	**83.7**	21.9	**69.3**	21.9	**75.2**
22.4	11.8	22.4	12.1	22.4	13.9
23.8	**23.0**	23.8	**22.8**	23.8	**24.9**
24.3	**100.0**	24.3	**100.0**	24.3	**99.8**
24.9	**29.4**	24.9	**22.8**	24.9	**26.1**
25.3	17.5	25.3	17.8	25.2	20.4
25.7	**26.0**	25.7	**28.5**	25.7	**29.8**
26.5	21.9	26.5	20.6	26.5	23.4
27.3	5.3	27.3	2.7	27.3	5.4
27.8	11.1	27.8	6.3	27.8	9.7
28.3	5.9	28.4	2.6		
28.6	7.6	28.6	2.7	28.6	5.4
29.0	8.0	29.0	1.7	29.0	6.0
29.6	8.6	29.5	4.8	29.5	5.2
30.0	12.5				
30.2	14.4	30.2	14.8	30.2	4.0
30.6	10.2	30.6	8.6	30.5	8.4
31.5	13.7	31.5	8.4	31.5	9.0
32.4	7.5	32.4	3.7	32.4	3.4
33.1	10.8	33.0	4.0	33.0	5.2
34.5	7.1	34.4	3.9	34.4	4.0
34.4	6.5	35.4	2.4	35.7	4.0

18. The few empty spaces in the Table above are not indicative of the absence of a diffraction peak in the relevant diffraction pattern at the referenced angles. Rather, as may be seen in the diffraction patterns at Tabs L and N, these empty spaces

correspond to areas of low intensity and closely spaced diffraction angles. As appears, the peaks not listed for the materials I made were masked by overlap with adjacent peaks. In addition, the identity of a crystalline sample is established with respect to a reference material if the scattering angles of the ten strongest reflections obtained for the sample agree to within ± 0.20 degrees with that of the reference material. See "X-Ray Diffraction," Physical Tests <941>, *The United States Pharmacopeia*, 24th ed., United States Pharmacopeial Convention, Rockville, MD, 1999, copy attached as Tab P. Applying the United States Pharmacopeia standard, where the bolded intensities in the Table above represent the ten highest intensity reflections, the crystalline paroxetine methane sulfonate materials I prepared are identical to the crystalline paroxetine methane sulfonate materials referred to in Examples 3, 4, 12, 14, 15, 16, 18, 19 and 20 of the '927 patent.

19. Based on the data summarized above, I conclude that the crystalline paroxetine methane sulfonate described in the '447 patent is identical to the crystalline paroxetine methane sulfonate described in the '927 patent.

20. I further declare that the above statements are true and that all statements made upon information and belief are believed to be true and furthermore that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under 18 U.S.C. § 1001, and may jeopardize the validity of this application or any patent issuing thereon.

1-17-2001
Date

Michael T. Crimmins, Ph.D.